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Freitag, Lutz ; Gördes, Martin ; Zarogoulidis, Paul ; Darwiche, Kaid ; Franzen, Daniel ; Funke, Faustina ; Hohenforst-Schmidt, Wolfgang ; Dutau, Hervé

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Towards Individualized Tracheobronchial Stents: Technical, Practical and Legal Considerations

Lutz Freitag[a] Martin Gördes[b] Paul Zarogoulidis[e] Kaid Darwiche[c] Daniel Franzen[a] Faustina Funke[c] Wolfgang Hohenforst-Schmidt[d] Hervé Dutau[f]

[a]Department of Pulmonology, University Hospital, Zurich, Switzerland; [b]Bess Pro GmbH, Medical Technology, Berlin, [c]Ruhrlandklinik, University Hospital Essen-Duisburg, Essen, and [d]Department of Cardiology, Nephrology, and Pneumology, ICU, Hof Clinic, Sana Clinics Group Northern Bavaria, University of Erlangen, Erlangen, Germany; [e]Pulmonary Oncology Unit, G. Papanikolaou, General Hospital, Aristotle, Thessaloniki, Greece; [f]Thoracic Oncology, Pleural Diseases and Interventional Pulmonology Department, North University Hospital, Marseille, France

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Customized airway stents · Additive manufacturing · 3D-printed stents · Drug-eluting stents

Abstract
Stent placement has been established as a standard procedure for treating airway obstructions. Other indications are localized malacias and fistulas. Though many different stents with various diameters and lengths are available, the shapes are hardly ever ideal because of the distorted anatomy in patients with diseased airways. There are technical and legal limitations for customizing purchased airway stents. Individually tailored stents would be preferable. New techniques of additive manufacturing such as 3D printing make it possible to produce optimized stents for a particular patient. Using CT data and bronchoscopic images, stents can be constructed that match a particular anatomical situation and apply the optimized expansion force. We give an overview of the currently available manufacturing techniques for polymeric stents and report about our own experience. Direct on-site printing of polyurethane stents in a hospital and printing individual extrusion molds for silicone stents in a certified cleanroom are both feasible. Furthermore, there are promising attempts of combining mechanically customized stents with surface modifications, drug-eluting features, biodegradability, and time-dependent adaptation (4D printing). Truly optimized airway stents with the potential of solving the well-known stent problems such as granulation tissue formation, remodeling, mucostasis, and infections are in reach. The technical hurdles are probably easier to overcome than the legal constraints. The legal situations are discussed from a physician's and a manufacturer's perspective.

Introduction

Bronchoscopic insertion of tracheobronchial stents is established as the standard of treatment option for patients suffering from central airway obstructions due to extrinsic compression. Often combined with resection

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E-Mail karger@karger.com
www.karger.com/res

Prof. Dr. L. Freitag
Hirslandenklinik St. Anna
St. Anna-Strasse 32
CH–6006 Luzern (Switzerland)
E-Mail freitag-hemer@t-online.de

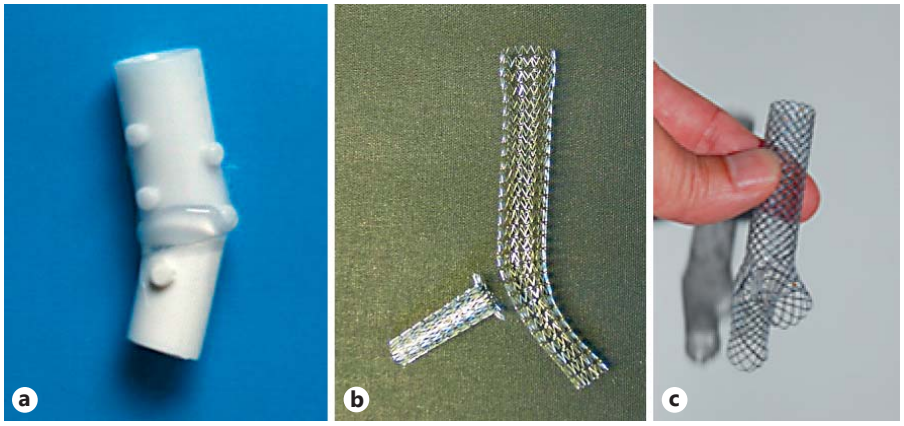

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Fig. 1. a J-stent "bedside made" by gluing together two Dumon stents with appropriate lengths, diameters and angle. **b** Custom-made nitinol stents for a patient with dehiscence by laser cutting and forming. **c** Individualized wire stent with modified angles and diameters for a patient with complex airway stenosis.

techniques such as laser or argon plasma coagulation, stents are placed to maintain airway patency by counteracting the constricting forces of tumors, lymph nodes or scar strictures as seen in benign stenosis. Other indications for stents are airway fistulas and dehiscences. In these cases, endoprostheses are placed to seal the trachea or bronchi against the esophagus or the pleural cavity [1, 2].

A plethora of stents from various materials are commercially available. Airway stents come in different lengths and diameters, are balloons or self-expanding, and are made from polymers or metals [2, 3]. However, almost all stents are straight and round-shaped. For regular cases, this is a reasonable compromise but frequently a more anatomically shaped, bended, twisted or tapered stent would be more appropriate. The trachea is basically horseshoe-shaped and the bronchi get more and more round-shaped after each branching [4]. Diseased airways are always deformed; in cases of benign strictures, they are typically triangular, slit or A-shaped [5, 6]. With the exceptions of bifurcated stents and Montgomery T-tubes, all stents are held in place by friction resulting from the expansion force they apply on the airway wall. This contact pressure impairs the microcirculation, which is most likely the main reason why granulation tissue develops [6–8]. Probably equally harmful are scratching movements of stent edges over the mucosa when the patient is breathing or coughing. In irregularly shaped stenotic areas, stents apply the highest pressure on the already damaged tissue (narrowest part), while the end parts move slightly over the originally healthy mucosa. Ideally, a stent would match the shape of the stenotic airway, adapt well and would exert different forces over its length in order to establish airway patency without creating further tissue damage. In some cases, only little structural augmentation is required while in others the stent must work against a powerful neoplastic compression or fibrous scaring. In order to seal fistulas, mild wall contact without stretching would be ideal. A possible solution would be a stent tailored to the particular anatomy with optimized expansion force varying over its length and circumference. In this technical paper, we outline how such a stent can be made using the emerging techniques of rapid manufacturing and 3D printing.

Past to Present

For the last 30 years, we had quite often encountered situations where normal stents could not solve the clinical problem. Examples are patients with pneumonectomies who had recurrences or stump fistulas. As J-shaped stents had not been available, we used tracheal and bronchial Dumon silicone stents which we cut and glued together (Fig. 1a). In the pioneering days of stenting, legal aspects did not play a role. Today, nobody would dare to insert a stent which had been produced with industrial silicone glue in the operating room. Fifteen years ago, the industrial partners had developed laser cutting techniques to produce tailored metal stents. They were produced after a patient-specific prescription and a sketch from the bronchoscopist. These stents had been made with the same validated manufacturing process as the standard stents. Delivery time was in the range of a few weeks and the costs could hardly be justified. Of course, these individualized stents had not undergone all the tests that their normal CE-marked family members had passed. Basically, it was a favor done by the industrial partners and the patient had abstained from his liability rights in order to get the best possible device based on the judgement of the

treating physician. The current step of evolution had been reached when stent manufacturers offered modifications of their existing products. The physician fills out a form and sends it to the stent manufacturer. Figure 1c shows as an example of a self-expanding bifurcated wire stent with limbs in different diameters and angles in two planes. We had implanted that particular stent in a girl with kyphoscoliosis who could not be treated with any off-the-shelf product. Similar problems were solved in patients with tracheobronchomegaly when we needed stents with extreme diameters (26 mm) or in patients with stump fistulas when we requested J-shaped stents with uncommon angles. This type of service is currently provided by manufacturers of silicone stents and wire stents in Europe. Usually, within 2–4 weeks after sending a prescription, the hospital receives a custom-made, sterilized stent for the individual patient at affordable costs. Standard instruments and insertion techniques can be used. However, the degrees of modifications are limited. All the currently available modified stents are still straight and round-shaped and they have a fixed expansion force. In order to get closer to the real anatomy, we have explored the techniques of 3D printing.

Present to Future

Basically, all established techniques of manufacturing are based on either subtractive, casting, deforming (reshaping) or additive techniques. Making a sculpture by removing parts of a stone until the desired figure remains is an ancient example of a subtractive process. Material is scraped, grinded, turned, or machined from a block in order to create the final product. Producing a coronary stent by cutting a nitinol tube with a laser is a modern example. The other basic manufacturing technique is shaping or molding. The principle remains the same, whether clay is formed to a dish or steel is pressed to a car wing. Both require considerable postprocessing including surface treatment until the desired function and appearance is attained. Finally there are additive techniques. Small pieces of materials are put together to create new stuff. Our ancestors managed to build a castle from stones and sand, students these days learn to build a smartphone. Especially this bottom-up principle seems to have no limits. In 1998, researchers at IBM moved 35 single Xenon atoms with a tunneling microscope to form the 3 letters of their logo. Theoretically, medical nanotechnology is able to produce anything including the ultimate tracheal stent; however, it is not available to everybody today.

Rapid prototyping with 3D printing techniques had rapidly revolutionized designing processes in the consumer industry during the last decade. In contrast to a simple computer-aided design (CAD) drawing displayed on a screen, a printed part allows a touch-and-feel experience as well as testing the mechanical handling feasibility of a future product. While in the beginning only model parts had been printed, we are now observing that more and more final products are made using the same techniques. Orthopedic surgeons print prostheses [9] and dentists teeth inlets [10]. It has recently been demonstrated that a tracheal cannula can be manufactured based on image data of a patient [11]. There is hardly any field in medicine that is not influenced by the new opportunities. The progress is so rapid that websites have been created which are almost daily updated in order to keep up with what is possible [12]. A landmark in pulmonary medicine was the creation of a biodegradable airway splint that was surgically implanted in a child with bronchomalacia [13, 14]. The design and manufacturing was a complicated process that involved several disciplines and took a long time. We have been looking for ways to produce a stent that can be inserted bronchoscopically hours or at max days after the problem has been detected. It should be customized regarding the individual anatomy and have optimized biomechanical features for the specific condition.

Technical Considerations

The process of creating customized stents with 3D printing techniques can be divided into the following steps.

Image and Data Acquisition

First, anatomical data are collected to design the shape of the device. They can be derived from CT images or from the drawing of a bronchoscopist. Using a modern multidetector computed tomograph, high-resolution 3D image data can be acquired within a single breath-hold. The data are processed, for example, to present a model on the screen that is usually called virtual bronchoscopy. The current state of the art regarding these image-processing techniques can be seen in navigation bronchoscopy systems. Specialized companies such as Materialise (Leuven, Belgium) provide services to help clinicians. Alternatively, measurements of stent-relevant dimensions can be made bronchoscopically and a simple drawing can be made by the endoscopist. This is certainly more de-

manding when it comes to drawing curvatures, angles, and orientations. For more complex situations, CT-derived virtual drawings are superior [15]. In the case of severe malacia, it could be of benefit to measure real-time diameter under simulation of different ventilation pressures and/or frequencies which can be done easily by jet catheter ventilation and cone beam CT-derived data acquisition [16]. In real clinical situations, a tumor will be removed and a stenosis will be dilated first. A preprocedure CT does not provide the data needed for the ideal stent. Length, shape and diameter of the diseased airway after the intervention will determine which stent dimensions are appropriate. Thus, at least a second CT performed after debulking and dilatation is necessary. Image data alone do not provide sufficient information about the rigidity of the airway structures and the technical feasibility of a stent insertion. The touch-and-feel information that only the bronchoscopist can deliver cannot be replaced by any image data.

CAD Designing

Following image acquisition and postprocessing, a 3D model is created with a CAD program. This is a critical step that requires the input of the treating physician. It would not help to design a stent that has the dimensions of the narrowed airway. After all, the stent shall counteract the constricting forces and open the airway. It would not be realistic either to create something that has normal diameters all along. The optimized prosthesis should match the dimensions of the nonaffected part but should be bigger at the location of the stenotic area. In addition, the expansion force should be greater at this location. Sealing a fistula, on the other hand, would be best accomplished with a soft and flexible part. For a stent made from a single polymeric material changing the tensile strength can only be accomplished by increasing the wall thickness. It is obvious that the treating physician must have the ability to stretch or bend parts of the virtual cast and determine the local strength. There are no established techniques to calculate or even estimate the compressing force of a stricture. It depends on the experience of the practitioner to select the optimal recoil. In the presented stents the local recoil can be influenced by the wall thickness. Thus, optimal stent designing software must provide the option to influence the material or the local wall thickness of the stent. This dream software should be able to import DICOM data but also have a smart user interface where the bronchoscopist who has done the examination and pretreatment (e.g., laser resection or balloon dilatation) can influence the prosthesis. After all, the bronchoscopist must be able to implant the optimized prosthesis with available instruments. The software interface must close the gaps between radiology data and practitioner expertise as well as between medical aims and practicability, which might be limited by material availability and engineering tools. Several groups are working on these types of modeling software for airway stenoses with a graphical user interface [16–18].

Generating a Construction File

In the next step, the model is electronically sliced into individual layers. A file containing this information is created that can be transmitted to a printer. This computer-readable file can be transferred in any way (CD or via the internet). A typical file format is STL. There are programs checking the file for plausibility, removing undesired overlays, closing possible gaps and adding support structures for free-standing or hanging parts. Finally, a device-specific code is generated that contains the instructions where and how much material shall be deposited.

3D Printing

The fourth step depends on the printing technology. Stereolithography printers use photopolymers that are cured by an UV laser. The above-mentioned external airway stent had been produced with this technique. Selective laser sintering uses a high-power laser to fuse small particles of thermoplastic, glass or metal. While these techniques are ideal for creating models with finest details, the list of available materials is still short and the devices are comparably expensive. In the pharmaceutical field, there are attempts to develop soft stereolithography materials that can carry and release drugs. In the foreseeable future, it should be possible to use these medical-grade photocured polymers for the production of stents. For the time being, the most common technique in 3D printing is fused deposition modelling. A thermoplastic material usually from a spool is heated, melted and extruded through a nozzle to form the 3D structure layer by layer. The printing material is deposited and bonded by the printer head until the final product can be removed. A second printer head can print support structures if needed. Precision and resolution are determined by the layer heights (typically 20–80 μm), material flow and other mechanical factors. With a semi-professional printer, wall thicknesses of 0.5 mm are easily achieved and a tracheal stent with 60 mm length and complex shapes is printed in roughly 2–4 h. We used the Ultimaker 2 (Ultimaker, Geldermalsen, the Netherlands) and a modified

DualX (2PrintBeta, Konstanz, Germany) in our laboratory for the experimental stents. We also got stents printed professionally by service providers (3D Medical Printing AG, Pfäffikon, Switzerland). Their high-end machines achieved higher precisions and smoother surfaces for the price of outsourcing and delays.

Surface Treatment

The fifth step is surface treatment of the stents. Grinding, polishing and dipping in solvents or liquid polymers have been used successfully. This depends on the printing material. In the beginning, when affordable printers became available, only semi-rigid materials such as acrylonitrile or polylactic acid could be used. Recently, truly flexible, rubberlike printing materials have become available enabling to print elastic stents with affordable and accessible equipment. Smoothing their surfaces without using toxic substances is not trivial. Before the prostheses can be implanted, they have to be cleaned. The remaining printing material, chemical solvents and any other potentially harmful stuff must be carefully removed.

Sterilization

Of course, nothing should be implanted that might be contaminated. Vapor-based sterilization techniques cannot be used since the melting temperature of most polymers is too low. Plasma or ethylene oxide processes are ideal and can be applied in most hospitals or industrial manufacturing facilities.

Materials and Customization

A common grouping of stents is based on the material they are made of. Even the reimbursement and coding systems distinguish between metal, polymer and hybrid stents.

Most modern metallic stents are made of nitinol, a shape memory alloy with superelastic properties. These stents are either woven from nitinol wire or cut out of a nitinol tube, then dilated and formed until they have the desired shape. Next, they are crimped down to a diameter that allows delivery through a catheter. After deployment, these self-expanding stents regain their original shape. Because of their favorable mechanical characteristics, nitinol stents have replaced older metal stents [1, 3, 19]. It is not possible to modify such a stent once it is inside its delivery catheter. Not even its length can be adjusted by the physician. Customizations as illustrated in Figure 1b have to be made by the manufacturer. Changes require reprogramming the cutting laser and the complete production of a forming tool, which makes this approach hardly feasible and very expensive.

The other classes of materials are polymers. These are long-chain molecules consisting of many small repeating units. The physical and biological behavior does not only depend on the chemical structure of the monomer but also on the degree of polymerization. Temperature has an influence on the tensile properties (how stiff, brittle or rubbery the material is and when it will break) [20]. Many different polymers are used in medicine, taking advantage of their specific properties. Hard contact lenses are made of polymethyl methacrylate, which is rigid, while tubes and drains are usually made from polyvinyl chloride, which is very flexible but not stretchable. Nondegradable suture threads are made from polypropylene because its high tensile strength and heart valves are made from polydimethylsiloxane, which is extremely flexible and has unmatched fatigue resistance. Polytetrafluoroethylene, known as Teflon, is extremely hydrophobic and has excellent lubricity. It might provide an ideal stent surface because no mucus would stick to it. However, polytetrafluoroethylene is very difficult to process and could not be modified for individual applications. For an airway stent we need a polymer that has an elastic modulus strong enough to counteract a tumor compression but enough flexibility to adapt to the complex shape of a trachea. It shall not rupture during the deployment procedure and shall not break after a few thousand coughs. Of course, it must be nontoxic and highly biocompatible, as well as bacteria-, water- and enzyme-resistant. For the use in a 3D printer, it should melt at reasonable temperatures (max. 240°C) and be stable at body temperature. These requirements limit the potential candidates to a much smaller group.

Nylon, a polyamide invented in 1935, is still used in surgical sutures. Nylon threads form the inner structure of the Polyflex™ stent (Boston Scientific). We have tried various Nylon filaments in our 3D printers. These printed stents felt somehow elastic but not as soft and malleable as we had hoped. They could not adapt sufficiently to irregular structures and transitions in the animal lungs and after initial tests, we abandoned this material for our project.

Polyurethane, which had once been developed as an alternative to Nylon, has similar mechanical properties. Thermoelastic polyurethane (TPE) is commonly used in medical products including coverings of airway stents. The Aero stent™ from Merit Endotek is a hybrid stent made from laser-cut nitinol with a flexible polyurethane

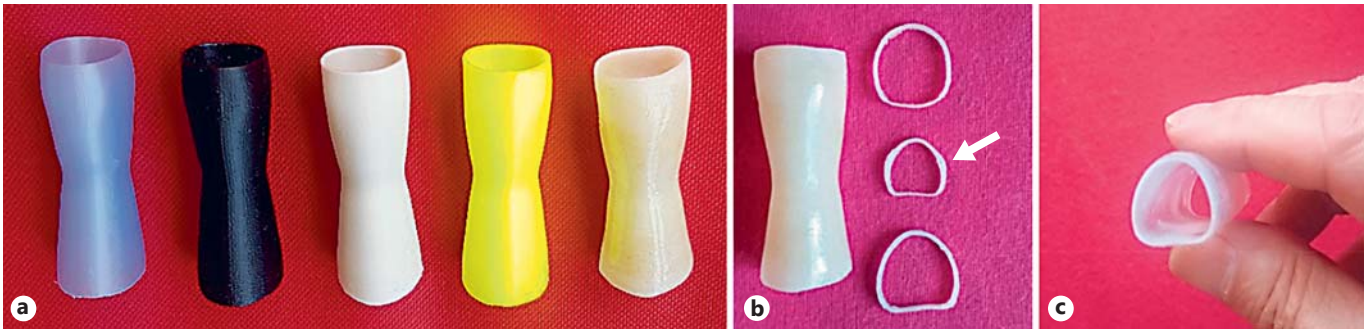

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Fig. 2. a Customized stent for hourglass stenosis directly printed with various thermoplastic polyurethane elastomers. **b** Note that the wall thickness is slightly higher in the constricted middle part (arrow), while the posterior membrane is thinner. Any variation of local wall thickness can be programmed. **c** Anatomically shaped silicone stent made by dipping a 3D-printed polylactide core in medical-grade silicone.

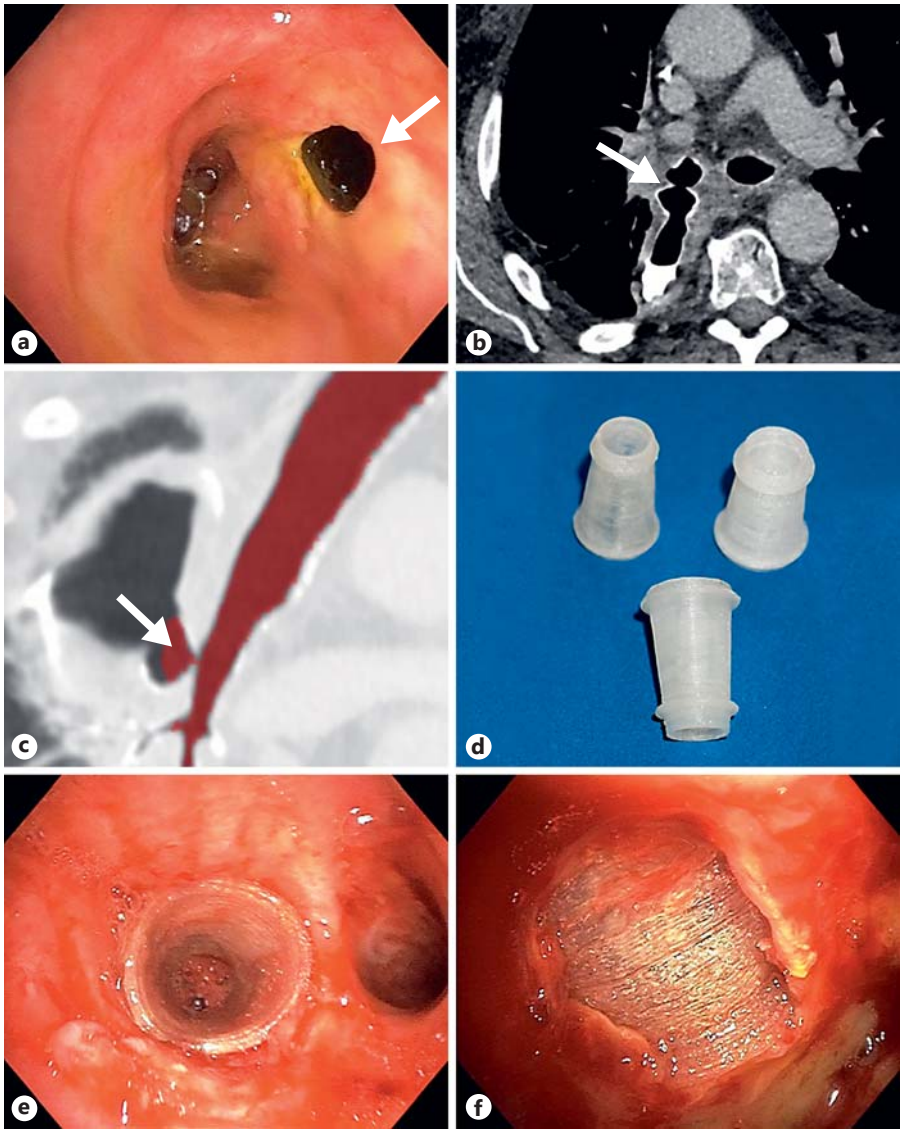

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Fig. 3. Gastrobronchial fistula in the bronchus intermedius after recurrence of esophageal cancer (arrow). Tapered bronchus below fistula opening. Bronchoscopic view (**a**), CT and "virtual bronchoscopy" (**b, c**). Tailored stent, 3D printed from polyurethane, tapered with "sealing" rings below and above fistula (**d**). Endoscopic views of sealing stent through the bronchus (**e**) and esophagus (**f**).

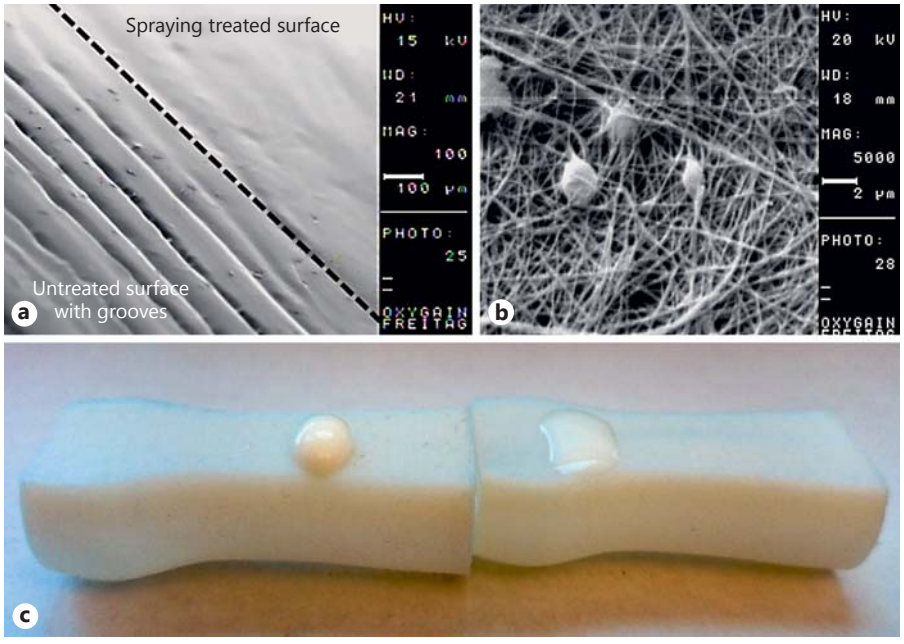

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Fig. 4. Surface treatments of anatomically shaped 3D-printed stents. **a** Electrospray coating for surface smoothing. Scanning microscope reveals smoothing effect of spray-coated polyurethane. In the untreated section (left lower corner), grooves from the print-head are clearly visible. **b** Surface of a polyurethane stent treated with antibiotic containing nanofibers produced by electrospinning. **c** Effect of nanocoating on wettability: the left stent is nanocoated and extremely hydrophobic, the right stent is untreated.

covering. Medical-grade TPE is available for 3D printing and we have printed a variety of prototypes as illustrated in Figures 2a and 3d. Using the fused filament printing technique, the stent can be printed in any shape with appropriate wall thicknesses (local tensile strength). The surface of such a printed TPE stent is slightly rough but once it has been dipped a few times in or sprayed with liquid solved polyurethane the surface gets smooth and slippery (Fig. 4a). These stents can be easily implanted using standard rigid bronchoscopes and pushers. We are currently evaluating whether they are not inferior compared to commercially available stents regarding mucus incrustations and biofilm build-up [20, 21].

Most polymeric stents are made from silicone; a few contain additional other copolymers and additives such as barium sulfate to achieve radiopacity. Due to the much lower modulus, silicone stents must have thicker walls than their metallic counterparts. The most popular stent is the one developed by Jean Francois Dumon easily recognizable because of their migration-preventing struts. They are cylindrically shaped and many diameters and lengths are available. Special models with 2 or 3 diameters for hourglass stenosis can be ordered. Physicians can slightly modify these stents on-site by cutting them to a desired length or punching side holes for the ventilation of a branching segmental bronchus [22]. However, changing shapes or transitions are not possible. J-shaped stents or stents with branches can only be made by the manufacturer and delivery times of weeks have to be accepted.

Custom-Made Silicone Stents

It is worth exploring how a typical silicone stent is made. Polydimethylsiloxane has been brought to market in 1943 by Dow Corning. Its flexibility, elongation property, tear strength, resistance, and excellent biocompatibility make it the almost ideal material for many medical devices including implants. At the beginning of the manufacturing process, silicone rubber is a highly adhesive gel or liquid. In order to convert it to a solid, it must be cured, vulcanized, or catalyzed. This is normally carried out in a two-stage process at the point of manufacturer. A typical medical silicone device is extruded or injection molded followed by a prolonged postcure process. Siloxanes, once cured, cannot be melted and extruded again. Therefore, medical silicone nowadays cannot be used in any of the available 3D printing processes. For the extrusion of silicone, normally stainless steel molding tools are used. Such molds are precision tools that are heavy, costly and take a long time to be manufactured. The steel molds need to be trimmed to achieve the desired output. A single silicone mold for serial production can easily cost a couple of EUR 10,000 even for fairly basic product designs. Producing customized stents in a mold suited for serial production is therefore economically and timely prohibitive. Low-temperature curing silicones may appear attractive but the production process is considered insufficiently reliable for implantable devices.

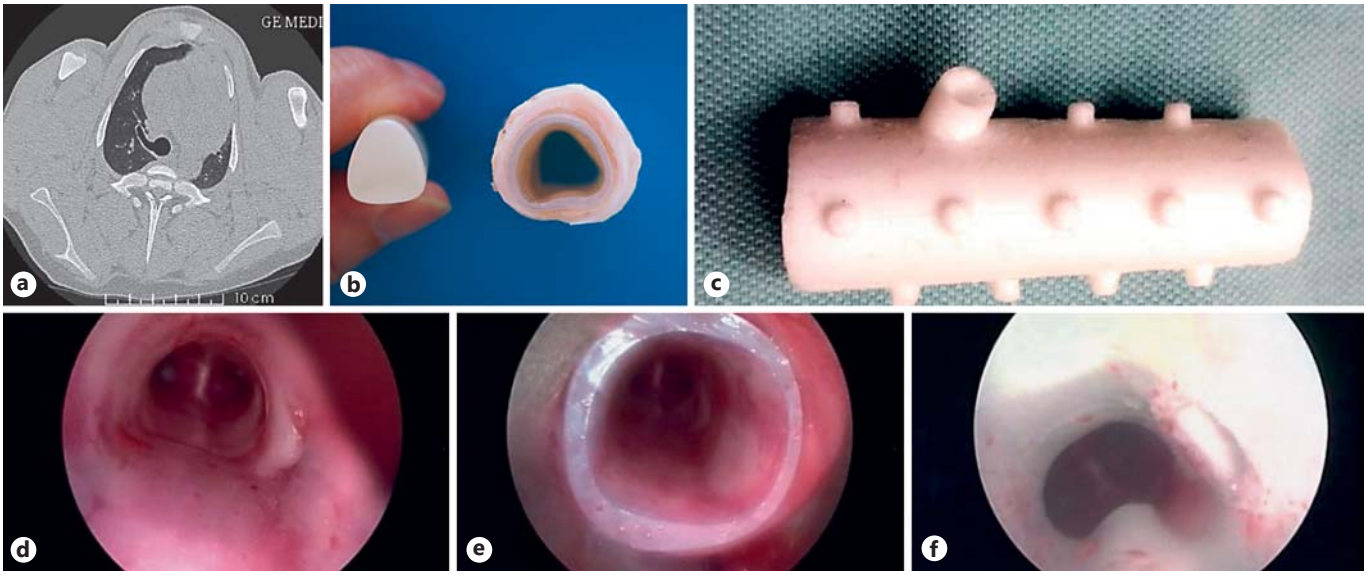

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Fig. 5. a–c Tracheal bronchus of a pig visualized by CT. Silicone stent made by printing a 3D core from acrylonitrile butadiene styrene and dipping in medical-grade silicone (**b**) produced in hospital or by professional injection molding (**c**). **d–f** Bronchoscopic image of a pig showing the tracheal bronchus (**d**), bronchoscopic images after insertion of hospital-made silicone stent (**e**) and injection molded silicone stent (**f**) with tracheal limb.

In order to overcome this limitation but still be able to mold customized silicone stents, we explored some transition technologies. We wanted to use silicone which is probably the best material but also use additive techniques that allow mold designs, which are nearly impossible to manufacture with traditional machine tools. The typical heat for curing silicone is somewhat below 200°C. Most thermoplastic materials suited for 3D printing will not tolerate such a condition. First experiments showed that the structure of printed devices and potentially open pore surfaces made demolding of the parts difficult. We considered using chemical additives but as the biocompatibility of the product might be negatively affected, we decided to avoid releasing agents. In our latest approach, we print only the core part of the mold (the "nest") and embedded it by a surrounding steel frame, so that the nest was not damaged by the excessive forces caused by the clamping force and the injection pressure. We reduced the molding temperature to a level that allows the silicone to stabilize its shape enough for removal from the mold, and then performed the actual curing and postcuring afterwards in an oven. As a proof of principle, anatomically shaped stents for pigs with a tracheal bronchus and dimensions derived from CT data were successfully produced in the manufacturing facility of the Bess Company. Seven days after submitting the STL files, we could implant these perfectly fitting silicone stents in pigs using the standard insertion instruments for Dumon stents (Fig. 5c).

Colleagues from Spain have developed programs [23] and designed a stent with the focus on ideal mechanical properties and have produced prototypes from medical-grade silicone activated by platinum catalyzers [24]. Colleagues from the Cleveland clinic have implanted a stent which they had manufactured in a similar way into a patient, early this year [25]. A group from Boston plans a clinical study with customized silicone stents according to an article in the Boston Globe [26]. Most recently, colleagues from France implanted a 3D planed molded silicone stent in a patient with a posttransplant complex airway stenosis [27]. All these groups use a two-step process to create a mold by a rapid prototyping stent technique and filling them with silicone. As explained above, these production methods require several days. However, according to a recent press release, the Wacker Company, a leading producer of silicone polymers, has developed a 3D printing process for silicone which still requires sophisticated apparatuses [28]. If this new technique could print medical-grade silicone directly in a desktop printer, it could become a true game changer. A directly printed silicone stent would be ideal for customization.

So far, we have shown that it is possible to produce customized stents with accessible technologies. Direct

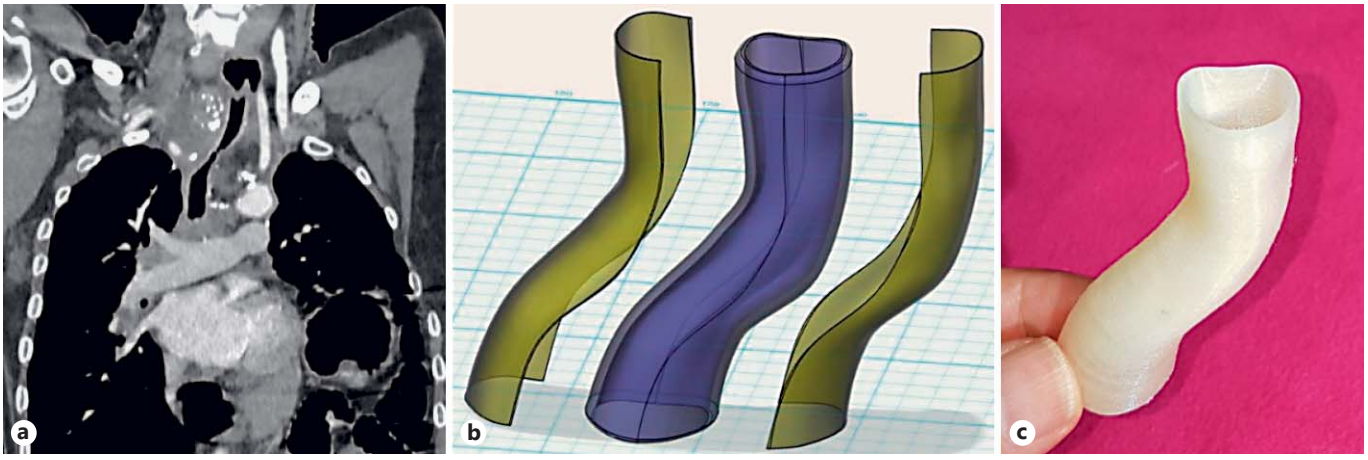

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Fig. 6. a Complex tracheal stenosis from tumor compression and postoperative distortion. **b** Image-based computer model for a 3D printer to print injection mold. **c** Tailored stent with individualized shapes and localized elastic hoop strengths made from medical-grade elastomer.

Table 1. Techniques, advantages, and limitations of various methods for productions of customized airway stents

Manufacturing method	Production location	Shape, dimensions	Shore hardness	Wall thickness, local recoil	Time to implant
3D printed with soft elastomer	on site in hospital	any	limited	completely variable	5 h
3D printed core silicone dipping	potentially in hospital	straight stents only	fixed	fixed	12 h
Silicone injection molded	device company	any	any	slightly variable	5 days

printing with elastomers is theoretically possible in any hospital. A physician could offer a solution for an airway problem within a few hours. For the time being, stents made of medical-grade silicone can only be made by molding machines, which requires engineering skills (Fig. 6). Manufacturing such a stent takes at least a week. However, patients with severe dyspnea cannot wait several days. Polyurethanes can already be printed and stents with acceptable quality can be produced within hours.

For a patient suffering from a huge gastrobronchial fistula, we constructed, printed and inserted such a custom-made stent. The spilling of bile and gastric fluid into a tapered bronchus intermedius could not be stopped with a commercially available stent. We printed the stent from polyurethane filaments with a tapered shape and sealing rings that isolated the destroyed wall from the bronchial system (Fig. 3). Using the dimensional data from a CT, the "production" of the stent took 5 h. The stent was easily inserted, the sealing was almost perfect and no side effects were observed.

Another option would have been to use the dipping techniques with platinum-catalyzed silicone. This is equally feasible for temporary prostheses but it is unclear whether such a production process will be ever accepted by regulatory authorities. Silicone rubber is probably the best material and a two-step process by 3D printing of a mold, followed by injection of medical-grade silicone and curing according to an approved protocol by a certified manufacturer seems to be most practical. All methods have advantages and disadvantages. The technical aspects are summarized in Table 1.

Future Perspectives

Mechanical Optimization

As already discussed, stents must cope with very different mechanical demands from mild structural augmentation to counteracting lateral tumor compressions or circular strictures from scar tissue. There are software tools that can predict the behavior of the device under

mechanical influences such as compression from specific points. The most commonly used technique is finite element analysis [24, 29]. Impressive color images show a what-if scenario and allow optimization during the design process. These tools are great if the parameters are known. Material constants, such as the elastic modulus and the wall thickness as well as all geometrical data from the prosthesis, can be fed in. However, the remaining unknown factor is the constricting force of the tissue as there are not feasible instruments that could measure these forces. Such a measuring tool would be very helpful. Our own experiments failed as the devices that we built were too fragile and could not be sterilized [30]. Some information about the tissue biomechanics can be gathered from imaging data but so far, there is no perfect solution. A Spanish group noted that the mathematical analysis for their stent optimization required high expertise and many hours of processing time on a high-power computer [24]. This is not practical for rapid action in a clinical setting and for the time being we have to accept some degree of uncertainty. However, the outlined approach of cooperation between the bronchoscopist who has examined the patient and "touched and felt" his airways and material engineers who know their tools and can influence the local stent properties is certainly a more promising approach than using the same stent with the same recoil for all indications.

Surface Treatment

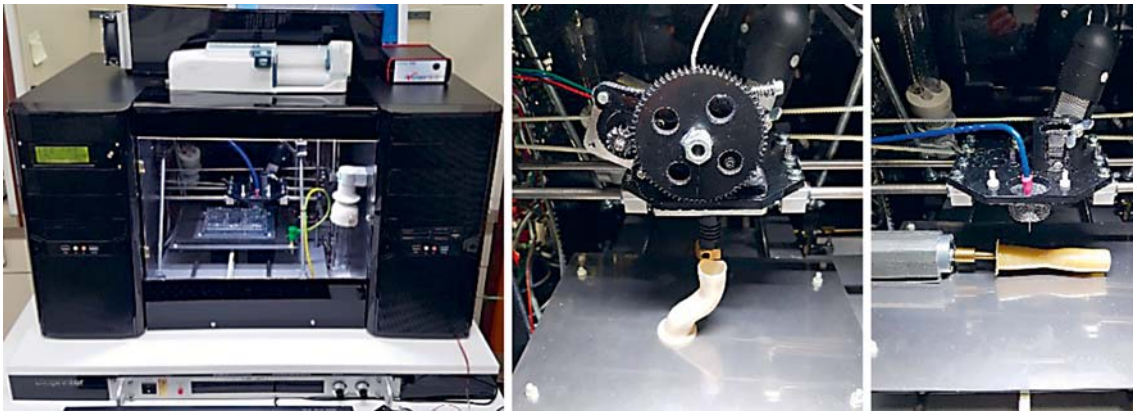
There are other approaches that will certainly merge with the presented 3D production techniques. As mentioned before, one of the most annoying problems with stents is the impaction or even incrustation with mucus. While Teflon stents will be difficult to make, plasma treatment or surface coating with repellent molecules can certainly be accomplished. The spray technique that we used for the stents in Figure 4 has broad applications in hygiene and household products. No mucus can stick to such a treated surface. However, these coating materials and sprays do not have any approval for medical implants. The same holds true for antibacterial coatings. Bacterial colonization and biofilm formation is a well-known problem with any type of implant [31, 32]. Surface roughness and porosity of implants probably facilitate microbial adhesions, biofilm build-up, and infections. Intrinsically antimicrobial polymers are attractive. They either repel or actively kill bacteria. Typical chain extenders of polyurethanes, e.g., hyaluronic acid or additives such as poly-N-vinylpyrrolidone, inhibit the adhesion of *Staphylococcus epidermidis* and *Staphylococcus aureus*. Active killing is accomplished by adding chemical substances (chlorhexidine), metal ions (silver) or antibiotics (minocycline, rifampicin) [33]. While these strategies have been followed extensively for intravascular prostheses, there are no comparable airway products. All major manufacturers of airway stents are reluctant to change their existing products. Technically, there are at least two feasible options for 3D-printed stents: silver nanoparticles or copper ions could be incorporated into the printing material, or coatings could be added after the product has been printed. Though such an approach might lower infection rates and prevent halitosis, gaining a CE mark or FDA approval would be too costly for the time being [34]. Mixing antibiotics into the above-mentioned materials would not be feasible as the melting temperature is too high. Another option would be combining the hot fused filament techniques (temperature approx. 200°C) or the injection mold technique with a secondary "cold" technique such as wet printing or electrospinning [35–37]. It has been shown that antibiotics can be incorporated in polymers and preserve sufficient antibacterial power. Technically, it is possible to add drugs, e.g., by electrospraying to the surface of a printed stent, even tailored to the particular infection strain of a patient as demonstrated in Figure 4c.

Drug-Eluting Stents

Obviously, the next step would be to transform a regular stent into a truly eluting device. Stents that release drugs over time are attractive in oncology [38] and could gain broad application. Tumor ingrowth into stents could be prevented. Incorporated antifibrotic drugs could target granulation tissue formation [39, 40]. The technical hurdles can be overcome even with low sophisticated equipment (Fig. 4, 7) but adding drugs to a stent which is a passive medical device would transform it into a pharmaceutically active product with more unsolved liability issues. It comes down to the same question, who would be legally allowed to fill such a device. Stent companies are not pharmaceutical companies and practitioners cannot take the responsibility either.

Biodegradable Stents

Regardless of how good a stent is, it remains a foreign body and will always have side effects. For some cases, it would be preferable to have a stent that vanishes over time in a predictable manner. Basically, a stent should disappear once it has accomplished its task without leaving traces. For the vascular system, several solutions are already available, while biodegradable airway stents are



Color version available online

Fig. 7. Self-developed 3D multimode, multimaterial printer, able to print and photocure various polymers and coverings with repellent substances or drugs and capabilities of robo spinning and electrospinning.

in their early infancy [12, 41, 42]. We are currently testing 3D-printed biodegradable stents in the animal laboratory.

Stents Changing over Time

3D printing is definitely not the last step in the evolution that we are observing. Further developments and modifications have the potential to create a truly new class of devices. Spatial adaption is certainly important. The optimized stent should adapt to the geometry as perfectly as possible. However, tissue conditions change over time. Any biological structure under pressure, whether a malignant tumor or a benign scar, has a viscoplastic behavior. Under the expanding force of a stent, a stenosis will slowly open and once it is wide enough, the friction is gone and the stent can migrate. A pediatric stent cannot grow with the child and will eventually become the limiting structure in an otherwise expanding trachea. Ideally, we would have a stent that changes over time, e.g., expanding a stricture slowly over several days or weeks. It would not rupture the tissue after deployment but would not migrate later on either. Shape memory alloys such as nitinol have the ability to recover to a former shape. We had tried stents that expanded to a desired diameter at body temperature. Technologically interesting, they had no advantages over self-expanding metal stents and none of these experimental devices has made it to clinical use. Polymers have a much greater potential [43]. Using smart polymers can advance 3D printing one step – or rather one dimension further. The new label is 4D printing. Devices can be printed with materials that can adapt and exhibit behavior in response to environmental changes or just over time. A simple example is presented in Figure 8.

Color version available online

Fig. 8. Approaches towards 4D stents. Combination of degradable and stable elastic polymers. Degradation of the restraining element makes a slowly dilating stent.

We printed a hybrid stent from an elastic polymer (polyurethane) and a second restricting polymer (polylactic acid) that degrades in vivo. This would be the simplest form of a "growing" stent. Other groups work on far more sophisticated technologies. Skylar Tibbits and his coworkers [44] have presented self-evolving 3D structures. Using a commercially available multimaterial 3D printer, they have created a straight wire that transforms itself into a cube when the temperature changes. Using new smart materials, it is possible to print and create objects that can exert forces and change shapes in predictable ways. Spatial and temporal adaptions can be programmed with biological aspects [45]. It will probably take a few years until these technologies will be accessible but there are already great opportunities using available devices and

materials. The opportunities seem endless. Anatomically shaped, smart responding, partially degrading, drug-eluting, antibacterially coated stents that are rapidly produced on-site can become clinical reality very soon. In cooperation with an engineering company (2PrintBeta), we have developed a very versatile multimode printer. This machine (Fig. 7) can not only print various polymers with the fused filament technique but it can also add coatings with polymers, nanoparticles, antibiotics, antiproliferative drugs and even cells. It has lasers for photopolymerization, motors for robo spinning and a high voltage source for electrospinning built in. This is still work in progress and we do not expect it to become a commercial product, but it helps to make our prostheses for experimental work.

Despite all optimism, we have to accept that stents are still foreign bodies. They do impair mucus clearance and they affect the tissue just by applying surface pressure. Regardless, how well we can design and produce a stent it will always be irritating. Tissue engineering techniques may one day allow to print true replacements for a diseased airway but for the time being can only try to optimize artificial prostheses. Many promising techniques are available; the limitations are mainly on the regulatory side.

Legal Aspects in General

The classical textbook on biocompatibility and performance of medical devices by Jean-Pierre Boutrand [46] emphasizes that only multidisciplinary approaches have chances to transform ideas into devices that can be implanted in patients. It deals with the obvious problem that we all expect new, superior devices, as soon as possible but also at least as safe as the existing ones. 3D printing is an example of this challenge in a nutshell. Using an amateur printer, we can make stents that fit better than any existing prosthesis but nobody wants to take the responsibility for possible device failures.

Fifty years ago, clinical anesthesiologists expressed their concerns about the safety of tracheal devices made from polymers. These physicians made suggestions and their initiatives helped to develop biocompatibility tests [47]. Today, any medical product has to undergo a battery of strict tests proving long-term safety [48, 49]. They are outlined in international standards and national guidelines for medical devices. ISO 10993 regulates the biocompatibility evaluation and tests required for devices that are directly or indirectly in contact with the body. The FDA follows the Medical Device Amendment of the US Food and Drug Act of 1976 and 1990 and requires even more in vitro and in vivo tests. Implanted stents fall in the category of implantable devices intended to be introduced into the human body and remain after the procedure. Of course, biological testing for chemical inertness, cytotoxicity, carcinogenicity, genotoxicity, and adverse immunological reactions are necessary to prove biocompatibility and biodurability of all used materials as well as the final product. Device efficacy and functionality including fatigue resistance, mucus accumulation, migration etc. are usually checked in meticulous laboratory bench tests and long-term animal trials. Without complying with the EU Medical Device Directive 93/42/EEC, no device may be sold or used in the EU.

For good reasons, regulatory authorities have taken over the responsibility and the initiative from physicians and inventors. As a result of these measures that have been put in place for risk minimization, the necessary paper work and the liability issues that would permit a clinician to develop and produce something for his patient are, mildly speaking, discouraging. There are problems in every step of the process. For example, the open access software package 3D Slicer 4.0 that is perfectly suited to import DICOM data, perform segmentation and export the files to load into the CAD program to generate the printer instructions has been developed by the National Alliance for Medical Image Computing, funded by the National Institute of Health. However, it states clearly that this software package is not an FDA-approved medical device. Using the pulmonary module of the Materialise Mimics Care Suite (Materialize, Brussels, Belgium), which is the best established software solution for medical printing in Europe, and following all recommendations does not mean that any further approval process could be skipped. None of the printers that we as physicians have access to does have approval for manufacturing of medical devices. The discussed printing materials do not fulfill the requirements that are standard in the pharmaceutical industry. The outlined processes of rapid additive production of a stent in a hospital setting are incompatible with current good manufacturing principles and ISO standards. Of course, the risk must be as small as possible but it is not justified to withhold help for a suffocating patient because there might be a potential side effect. Some loop holes might exist that would allow manufacturing a temporarily used device in a hospital that would help a patient for a few days. Swiss regulations, for example, permit these types of experimental therapies, if two independent disciplines state that there are no other

treatment options. However, stents for long-term use must be produced under good manufacturing principles conditions. For the particular problem of 3D-printed devices, the FDA has had a hearing and has provided suggestions how the process could be facilitated without jeopardizing the patient's safety [50]. None of these recommendations has any binding legal power but a process has been started [51]. To our knowledge, European authorities have not released any helpful guidelines, neither for practitioners nor for industrial partners.

Legal Situation (Europe) for a Professionally Manufactured Individual Stent

To bring a customized stent to the market, the medical device manufacturer must meet a couple of requirements. Even if a specific stent design is prescribed by the physician, the manufacturer must assure that the stent is properly manufactured and fulfills the essential requirements for a medical device. These essential requirements are defined in Europe by the European Medical Device Directive (MDD, annex I). In annex VIII of the MDD, the necessary documentation for a custom-made device is defined.

Basically, custom-made devices do not carry a CE mark but the words "custom-made device." The manufacturer provides basic information about the product and warrants that the so-called essential requirements are fulfilled. The fitness of the stent for the particular indication of that individual patient lies within the responsibility of the physician. The manufacturer holds detailed records on file for the competent authorities, in case of custom-made stents for a period of 15 years. Further local requirements may occur. To be able to demonstrate that a product fulfills the essential requirements, the manufacturer typically has to maintain a quality assurance system that includes design and production controls. Design controls for instance require strict adherence to risk management standards, standards for product safety (e.g., biocompatibility), or product-specific type of standards. Product performance tests and data are also part of the design controls. Production controls include all sorts of production environment requirements (e.g., cleanroom), sterilization, raw material control, avoiding production and labeling errors, etc. All relevant production steps are subject to validation and inspection procedures.

It is the responsibility of the competent regional authority to keep custom-made manufacturers under their surveillance. So, even if custom-made products do not carry a CE mark, there are practically the same regulatory requirements to fulfill and the same level of general product safety to achieve.

Summary and Outlook

It has been shown, that the use of 3D printing techniques is capable of manufacturing custom-made devices made of silicone or elastic thermoplastics. 3D printing technologies are accessible for physicians. An optimized stent could be produced in a normal hospital laboratory. It could be surface coated and even drug eluting. Though technically feasible, liability issues will probably make this approach impossible. A reasonable compromise would be to provide software tools that would enable the bronchoscopist to create an instruction file in an interactive manner and send this file to a certified manufacturer who produces and sterilizes this tailored stent. This specific process enables the practitioner to receive a stent, which is perfectly adapted to the indication in a fast way and with reasonable costs. Additionally, it is possible to manufacture products with geometries, which are almost impossible to manufacture with existing processes. However, there are still many open questions. Not only the biocompatibility and stability of the finished products has to be guaranteed, but also the design and manufacturing processes have to be validated and optimized to achieve a reproducible and safe product. Adding further features such as biodegradability, controlled drug release or predictable deformation (growth) is technically feasible but the legal pathways are huge hurdles and the costs involved might prevent industry partners from addressing the unmet need of a truly optimized airway stent. Continuing (US) or starting (Europe) a constructive dialog between physicians, manufacturers and regulatory authorities is most needed.

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